REMARKS

Claims 1-7 and 14-29 are currently pending. Claim 8 is canceled without prejudice and new Claims 16-25 are drawn to the subject matter of former Claim 8. New Claims 26-29 are supported by the specification at page 3, lines 3-9, and in the examples in which no addition of phospholipids is conducted. No new matter has been added herewith. The following addresses the substance of the Office Action.

Claim Objections

Claim 8 was objected to because it was drawn to the method of 1 or 3. Claim 8 was also objected to under 37 C.F.R. § 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 8 is canceled, thereby rendering the objections moot.

Obviousness

Claims 1-6, 8 and 14 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Kraus et al. (U.S. Patent No. 5,143,838) in view of Anderle et al. (U.S. Publication No. 2003/0133829). The Examiner acknowledged that Kraus does not teach solvent/detergent inactivation of the prothrombin complex prior to conversion on an anion exchange medium. The Examiner believes that the step would be obvious in view of the teaching of Anderle, which teaches a gentle, effective procedure for inactivating pathogens in a protein solution. However, even if these two references were combined, the order of steps recited by the pending claims would not necessarily be obtained. As explained in further detail below, this order of steps is critical in achieving the results of the present invention.

Background

By way of background, solvent/detergent (S/D) treatment is accepted by those in the field as describing a method of virus inactivation which disrupts the lipid envelope of certain viruses. The application as filed specifically acknowledges that such techniques are known in the art (see page 1, lines 30-36 of the application as filed). Furthermore, it was known before the priority date of the present application that S/D treatment is generally tolerated by blood proteins, and it was a commonly used method for virus inactivation of blood products intended for clinical application (see page 2, lines 9-11 of the application as filed). However, a known problem was that once subjected to solvent/detergent treatment, the protein prothrombin (also known as factor

II) could not be activated to thrombin effectively. As indicated on page 3, lines 10-13 of the present application as filed, the present invention has overcome these problems to provide a method for the preparation of thrombin from prothrombin which has undergone a solvent/detergent virus inactivation step to remove enveloped viruses.

The present invention solves this problem by providing a process according to the present independent claims. In particular, pathogens in the plasma solution are first inactivated using solvent/detergent (S/D) inactivation. The inactivated solution is then loaded onto an anion exchange medium, the anion exchange medium is washed to remove the solvent-detergent medium, and the prothrombin is then activated on the anion exchange medium by the addition of metal ions.

The efficacy of the method of the present invention at activating prothrombin obtained from an S/D-treated thrombin solution is shown in Example 9 of the application as filed. Samples B and C in Example 9 demonstrate that negligible thrombin can be generated from virus inactivated (solvent/detergent treated) prothrombin complex in solution. However, sample A of Example 9, which is subjected to the process according to the present invention, demonstrates that high levels of thrombin can be generated if the virus-inactivated prothrombin complex is loaded onto an anion exchange medium in the manner claimed.

Kraus

Kraus seeks to address the previous difficulty of producing thrombin from plasma or a plasma fraction in a single step (column 1, lines 43-57). Kraus et al. identifies previous methods as requiring several steps including: (1) preparation of a prothrombin complex from the plasma or plasma fraction; (2) prothrombin activation to thrombin; and (3) subsequent purification of the thrombin from other components. Kraus identifies the complexity and poor yields (i.e., 20,000 to 40,000 units per liter of plasma) of previous methods as the problem to be overcome.

The Kraus method achieves up to 90,000 units of thrombin from one liter of starting plasma, and the thrombin purity (specific activity) is up to 1400 units per mg of protein (Kraus et al., Column 2, lines 14-18). However, Kraus also alludes to two deficiencies in the method disclosed therein (column 2, lines 58-69): a further concentration step is required to achieve potencies greater than 100 units per mL; and a further chromatography step is required to achieve specific activity (purity) of greater than 2000 units per mg. Thus, the "one-step" teaching of Kraus et al. actually requires at least three steps to produce the thrombin product generated by the

process of the present invention in a single step. Each additional step in the Kraus preparation process will incur a loss of yield.

While the Kraus reference does disclose that virus inactivation can be undertaken before or after thrombin is isolated from the plasma or plasma fractions, there is no disclosure or suggestion that virus inactivation could be carried out on prothrombin. This is consistent with the knowledge in the art at the time that virus inactivation using the solvent/detergent method should be carried out after the prothrombin has been activated to form thrombin because factors such as the phospholipids, which are necessary for the activation reaction, would be eliminated by the S/D treatment. See page 2, lines 18-29 of the present application as filed. Therefore, the skilled person reading Kraus would not have expected that solvent detergent virus inactivation could in fact be carried before the prothrombin was activated to form thrombin.

Anderle

Anderle teaches a method for inactivating pathogens in a protein solution. As indicated in paragraph [0058] of Anderle, in addition to the S/D methods, the reactive protein may be enriched or further purified either before or after the S/D treatment. However, Anderle does not supply any teaching that S/D treatment can be used to inactivate viruses in a prothrombin complex prior to loading onto an anion exchange medium.

It is noted that paragraph [0083] of Anderle refer to the FEIBA (Factor Eight Inhibitor By-passing Activity) assay, which measures the protein's potential to correct prolonged clotting time in plasma which contains inhibitory antibodies to factor VIII. However, paragraph [0078] of Anderle clearly indicates that the FEIBA is derived from an auto-activated prothrombin complex, which is then subjected to S/D treatment in Examples 6 and 7. Thus, FEIBA is present prior to S/D treatment. The described "generation of FEIBA" after solvent/detergent treatment in paragraph [0082] of Anderle actually describes the FEIBA functional activity assay and not the manufacture of product with FEIBA itself. Accordingly, Anderle does not demonstrate that prothrombin activation can be performed after solvent/detergent treatment.

Combination of Kraus with Anderle

In view of the foregoing, the combination of Anderle with the Kraus reference, would not suggest to one having ordinary skill in the art that S/D inactivation of viruses of a prothrombin complex should be conducted prior to anion exchange, as in the claimed invention. Indeed, conducting this step in the manner claimed would be contrary to the knowledge in the art at the

time that virus inactivation using the solvent/detergent method should be carried out after the prothrombin has been activated to form thrombin. As such, the combination of Anderle with Kraus is not sufficient to create a *prima facie* showing of obviousness.

The combination of Anderle with Kraus is even further deficient in creating a *prima facie* showing of obviousness with regard to Claims 26-29, in which no phospholipds are added. As stated above, the knowledge in the art at the time of the invention was that factors such as phospholipids are necessary for the activation reaction would be eliminated by the S/D treatment. This is supported by the disclosure of Dr. Karl Landsteiner described in Applicants' specification at page 3, lines 3-9, in which activation of S/D treated prothrombin to form thrombin was only successful in the presence of added phospholipids. Nothing in either of Anderle or Kraus would lead one having ordinary skill in the art to activate prothrombin without addition of phospholipds. Accordingly, no *prima facie* showing of obviousness of new Claims 26-29 can be established by the combination of Anderle and Kraus for this additional reason.

Unexpected Results

Even had a proper *prima facie* showing of obviousness been set forth by the references cited, the present invention provides significant unexpected results that would rebut any such showing. In particular, the presently claimed invention provides both a purity and concentration of thrombin, which are surprisingly better than those achieved by the Kraus reference.

The skilled person understands that protein purification methods offer a choice between yield and purity. Thus, yield may be sacrificed to achieve desirable purity (because impurities can cause adverse reactions in patients treated with thrombin). Even if yield is sacrificed, the process of the present invention produces a higher purity product at a given yield when compared to the process disclosed in Kraus.

The Kraus reference discloses that a specific activity (purity) of approximately 800 to 14000 units/mg of protein can be directly obtained using the methods disclosed therein. In order to achieve higher purity, additional purification steps, such as cation exchange must be conducted. See Kraus at column 2, lines 61-67. In contrast, the Examples disclosed in the present specification describe the production of a product having greater than at least 2000 units/mg of protein without the need for cation exchange chromatography or other purification steps, which can diminish yield.

Kraus does not directly specify the concentration of the thrombin obtained in the process disclosed therein. However column 2, line 58 of Kraus indicates that the concentration can be increased to more than 100 units per mL by known methods e.g., ultrafiltration. Thus, the concentration that is directly obtained from the methods described by Kraus are necessarily lower than 100 unites per mL. It is noted that the Examiner incorrectly describes this step as a purification; it is actually a concentration step. Such concentration methods are used in the pharmaceutical industry, but are cumbersome, expensive and time-consuming. Such a step would eliminate the benefits claimed in Kraus of single step processing from plasma or plasma fraction.

In contrast to the relatively low concentrations obtained by Kraus, the present invention provides a high thrombin concentration of more than 900 units per mL without the need for further processing steps. The following table summarizes the calculation of the concentrations obtained in the examples:

Example	Thrombin	Column diameter	Column Height	Column bed volume (BV)	Elution volume		Thrombin
	MIU	cm	cm	mL	BV	mL	IU/mL
1	2.8	5	13	255	11	2808	997
14	2.2	5	13	255	9	2297	957

In conclusion, the presently claimed methods provide a novel means to prepare thrombin from prothrombin, after pre-treatment of prothrombin with detergent to inactivate virus. The process yields both an unexpectedly high purity and unexpectedly high concentration of thrombin. In contrast, extra steps are needed to produce thrombin by the Kraus method to achieve the same purity and potency as that obtained using the process of the present invention incur a yield penalty, which would eliminate any upstream yield benefit. The necessary extra steps undermine the notion that the Kraus process has overcome the problem of multiple step processes for the preparation of thrombin. Based on the foregoing remarks, the claimed methods of the present application provide unexpected advantages over Kraus in view of Anderlie et al. As such, the unexpected results achieved by the presently claimed methods rebut any alleged *prima facie* obviousness in view of the cited references.

Claims 7 and 15 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Kraus et al. (*supra*) in view of Anderle et al. (*supra*) and in further view of Kingdom et al. (U.S. Patent No. 5,354,682) and Heimburger et al. (U.S. Patent No. 6,346,277). However, since Claims 7 and

15 are ultimately dependent on Claims 1 and 3, they are not obvious in light of the remarks above.

Accordingly, the Applicants respectfully request removal of the rejections under 35 U.S.C. § 103(a).

Double Patenting

Claims 1 and 6 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 14 and 21 of copending Application No. 10/520,436. However, Claims 14 and 21 were canceled from application No. 10/520,436 in a response submitted on October 30, 2008 to a Restriction Requirement in that application. Thus, the provisional rejection is rendered moot.

Alternatively, as neither application is yet in condition for allowance, Applicants request that the Examiner hold this double patenting rejection in abeyance until such time as either Application No. 10/520,436 or the present application is otherwise in condition for allowance.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

In view of Applicants' amendments to the Claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: November 26, 2008

By: _____

Raymond D. Smith
Registration No. 55,634
Agent of Record
Customer No. 20995
(949) 760-0404

6285685
112508